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Advanced interatrial block is a surrogate for left atrial strain reduction which predicts atrial fibrillation and stroke

Juan Lacalzada-Almeida[1] | María Manuela Izquierdo-Gómez[1] | Javier García-Niebla[2] | Roberto Elosua[3,4] | Alejandro Jiménez-Sosa[5] | Adrian Baranchuk[6] | Antonio Bayes de Luna[7]

[1]Department of Cardiology, Hospital Universitario de Canarias, Tenerife, Spain
[2]Servicios Sanitarios del Área de Salud de El Hierro, Valle del Golfo Health Center, El Hierro, Spain
[3]Cardiovascular Epidemiology and Genetics Research Group, IMIM (Hospital del Mar Medical Research Institute), Barcelona, Catalonia, Spain
[4]Facultad de Medicina, CIBER Cardiovascular Diseases (CIBERCV), Universidad de Vic-Central de Cataluña, Vic, Spain
[5]Research Unit, Hospital Universitario de Canarias, La Laguna, Santa Cruz de Tenerife, Spain
[6]Heart Rhythm Service, Kingston General Hospital, Queen's University, Kingston, Ontario, Canada
[7]Fundación Investigación Cardiovascular, Institut Català Ciències Cardiovasculars, Barcelona, Catalonia, Spain

Correspondence
Juan Lacalzada-Almeida, Cardiac Imaging Laboratory, Department of Cardiology, University Hospital of Canary Islands, Tenerife, Spain.
Email: jlacalzada@gmail.com

Abstract

Background: The association between advanced interatrial block (aIAB) and atrial fibrillation (AF) is known as "Bayes' Syndrome." There is little information on the prognostic role that new speckle tracking echocardiographic (STE) imaging techniques could play in it. We have examined the relationship between left atrial (LA) STE and the prediction of new-onset AF and/or stroke in IAB patients.

Methods: This is an observational prospective and unicentric cohort study with 98 outpatients: 55 (56.2%) controls with normal ECG without IAB, 21 (21.4%) with partial IAB (pIAB) and 22 (22.4%) with aIAB. The end point was new-onset AF, ischemic stroke and the composite of both.

Results: During a mean follow-up of 1.9 (1.7–2.3) years, 20 patients presented the end point (18 new-onset AF and two strokes): 8 (14.5%) in the control group, 3 (14.3%) in pIAB and 9 (40.9%) in aIAB, $p = 0.03$. In multivariable comprehensive Cox regression analyses, a decrease in absolute value of strain rate during the booster pump function phase (SRa) was the only variable independently related to the appearance in the evolution of the end point, in the first model (age, P-wave duration and SRa): HR 19.9 (95% CI, 3.12–127.5), $p = 0.002$ and in the second (age, presence of aIAB and SRa): HR 24.2 (95% CI, 3.15–185.4), $p = 0.002$.

Conclusions: In patients with IAB, a decrease in absolute value of LA SRa with STE predicts new-onset AF and ischemic stroke. Future studies should confirm our results and assess the prognostic usefulness of LA STE in patients with IAB.

KEYWORDS
interatrial block, new-onset atrial fibrillation, speckle tracking echocardiography, stroke

1 | INTRODUCTION

Bayés de Luna et al. described the electrocardiographic and vectocardiographic criteria that identify interatrial block (IAB) and its relationship with atrial fibrillation (AF), as Bayes Syndrome (Conde et al., 2015). There are two types of IAB, partial (pIAB) and advanced (aIAB). In the pIAB, the stimulus is delayed between the two atria, but can cross the septum via the Bachmann's bundle region. In this region, the conduction of the electrical stimulus is totally blocked in patients with aIAB (Bayés de Luna et al., 1988; Figure 1). Transthoracic speckle tracking echocardiography (STE) has shown that a decrease in strain and strain rate (SR) absolute value during the booster pump function phase (SRa) of the left atrial (LA) and during the LA reservoir phase predict the development of new-onset nonvalvular AF (Hirose et al., 2012), progression of paroxysmal AF to persistent or permanent (Yoon, Oh, Kim, Park, & Kim, 2015) and

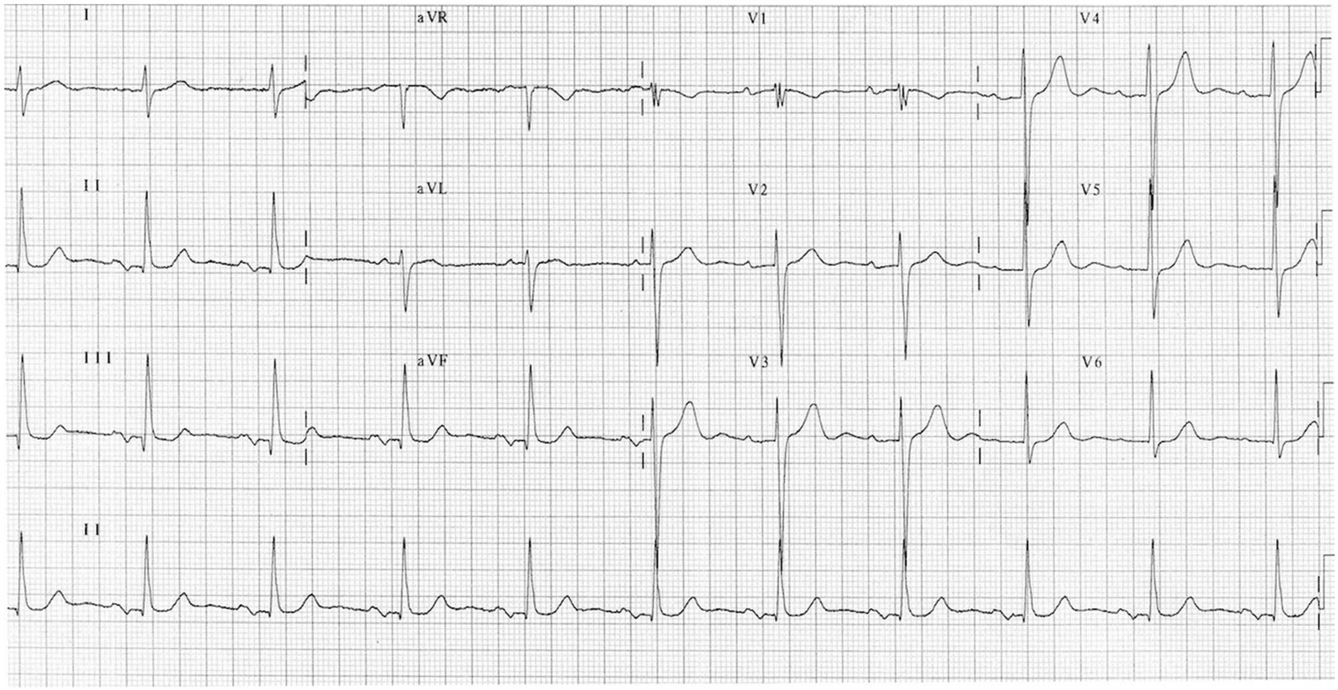

FIGURE 1 Electrocardiogram of a patient in our series showing an advanced interatrial block

recurrence of AF after radiofrequency catheter ablation (Montserrat et al., 2015). Recently, STE described that patients with IAB show a decrease in SRa (Lacalzada-Almeida et al., 2018). The objective of the present study was to evaluate the relationship between STE of LA and the appearance of AF or stroke in patients with IAB.

2 | METHODS

2.1 | Patient population

This is a prospective, unicentric observational cohort study, January–May 2016, with 98 outpatients over 60 years of age, scheduled for preoperative ECG of noncardiac surgery. All patients underwent a medical history, ECG and STE at the time of inclusion in the study. Patients with a history of supraventricular arrhythmia verified from their hospital admission, emergency records or long-duration ECG Holter monitoring were excluded.

2.2 | Electrocardiogram

The 12-lead ECG was performed according to established standards (Kligfield et al., 2007). One experienced operator blinded to the TTE and STE data analyzed the ECGs. The P wave was measured in the frontal plane leads recorded at the same time, with digitized ECG using GeoGebra 4.2 software. The ECG image was amplified up to 20 times its original size to define the interval between the earliest and the latest detection of atrial depolarization, defined as a positive or negative deflection, respectively, that deviates from the baseline before the QRS complex. The software allowed us to measure the distance between the earliest and the latest detection of atrial depolarization, which was then converted to ms. The partial IAB (pIAB) is shown as a P wave of ≥120 ms (Figure 2a) and the advanced IAB (aIAB) as ≥120 ms P wave with a biphasic or ± morphology of the P wave in leads II, III and aVF of the ECG (Figure 2b). Participants were categorized into three groups of interest based on the ECG: control patients with normal ECG without IAB, patients with pIAB and patients with aIAB.

2.3 | Echocardiography

Echocardiograms were digitally stored and analyzed by two experienced operators blinded to the clinical ECG data, using a commercial system iE33 xMATRIX, Koninklijke Philips NV, Eindhoven, The Netherlands, with a 2–4 MHz multifrequency transducer. Three consecutive beats were recorded during apnea in a cine-loop format. The analysis was performed using an echocardiographic analysis system (Xcelera R2; Philips). LA measurements and Doppler variables to quantify left ventricular diastolic function were measured according to standard echocardiographic methods (Lang et al., 2015; Nagueh et al., 2016). For STE of the LA, standard two-dimensional images from apical four- and two-chamber views were acquired, with a narrow sector angle (30°–60°) and a frame rate of 60–90 frames per second. The LA endocardial border was manually traced using the point-and-click technique, marking two points at both ends of the mitral annulus and a third at the ceiling of the LA, in end systole (Figure 2c,d). The surface epicardial tracing is automatically generated by the system and can be adjusted manually by the operator in cases of tracking failure. Any segments that subsequently failed to track were excluded. The LA myocardium was divided into 12 segments of interest for analysis, and

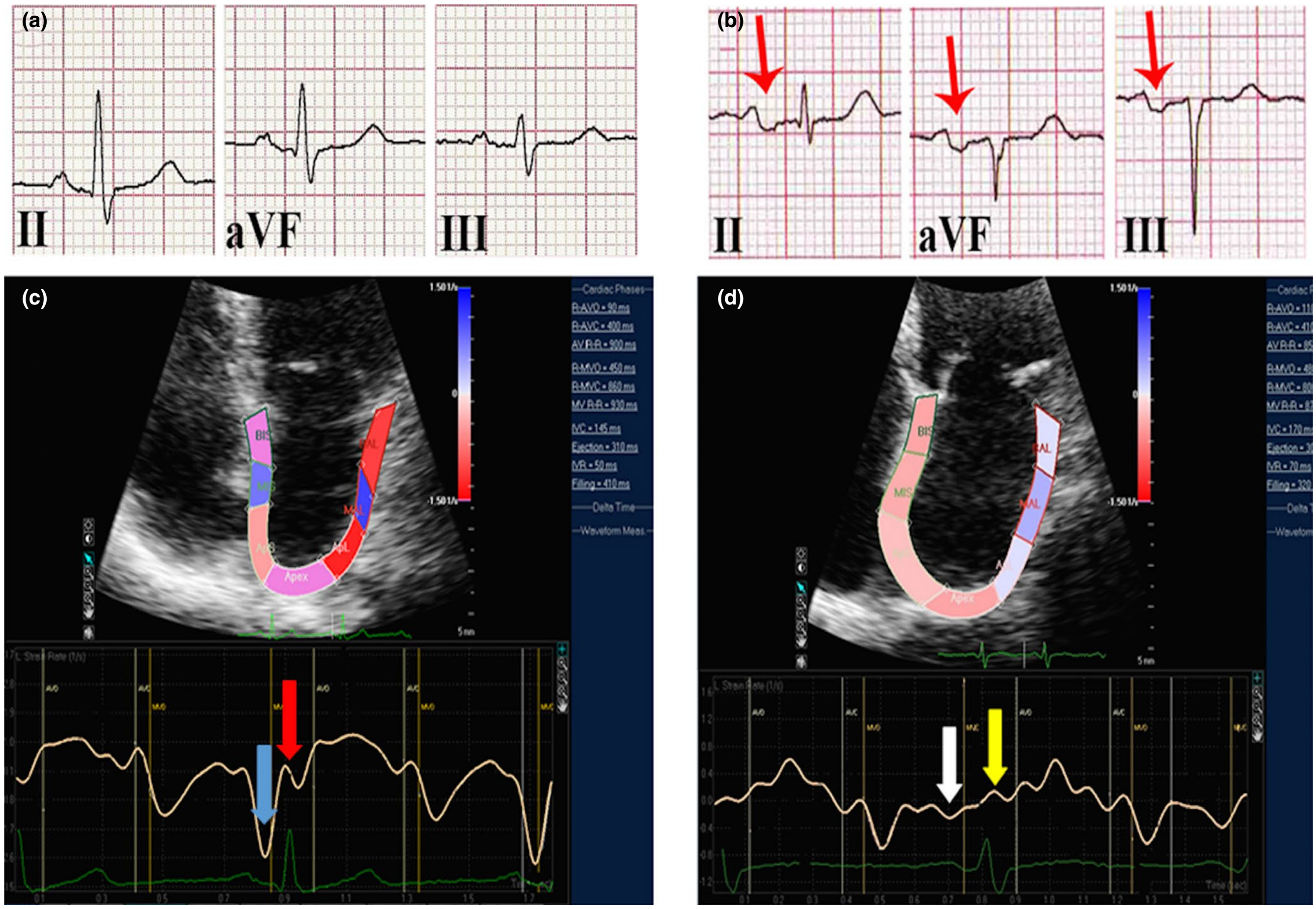

FIGURE 2 Comparison of ECG and speckle tracking echocardiography of a normal subject and another with advanced interatrial block. ECG (a) and left atrial (LA) strain rate (SR) echocardiography (c) in normal subjects, with normal SR of LA contraction (blue arrow) and reservoir (red arrow) phases. ECG with advanced interatrial block (b); red arrows show biphasic or ± P-wave morphology and with decreased SR of LA contraction (white arrow) and reservoir (yellow arrow) phases (d)

longitudinal strain and SR were measured automatically "offline," using the QLAB Advanced Tissue Motion Quantification (Philips) Release 8.1, equipped with STE analysis software. Global longitudinal strain and SR were the averages of the 12 values obtained for each LA segment (Yasuda et al., 2015). Since the primary variable of interest was the contractile function of the LA, the beginning of the cycle was arbitrarily chosen as the beginning of the P wave of the ECG (Vianna-Pinton et al., 2009).

2.4 | Follow-up and outcomes

All patients were evaluated biannually with clinical history and ECG, after being included in the study. The end point was defined as new-onset AF, defined as the first documented episode of AF, ischemic stroke and the composite of both (Escobar-Robledo et al., 2018).

Informed consent was obtained from each patient, and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Clinical Research Ethics Committee of the University Hospital of the Canary Islands (Tenerife, Spain).

2.5 | Statistical analysis

Continuous variables were reported as means and *SD* or as medians and interquartile ranges according to the nature of the variables. Categorical variables were reported as frequencies and percentages. Comparisons of continuous variables between groups were carried out using the one-way ANOVA test or Kruskal–Wallis test as appropriate. Categorical variables were presented as frequency and percentage and were compared using Fisher exact or chi-square tests. Correlations were obtained using the Spearman rank test. Survival analysis was performed using Cox's proportional risk model for single events and a multivariate backward stepwise regression analysis, adjusting for potential confounders, including those variables that proved significant on univariate analysis. The ability of the SRa to correlate with the presence or absence of the end point was verified using receiver operating characteristic (ROC) curves. A 2-tailed p value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed using SPSS for Windows, version 23 (SPSS Inc., Chicago, IL, USA).

TABLE 1 Baseline characteristics according to the presence or absence of end point (atrial fibrillation and/or stroke in the evolution)

Variables	Group with end point (n = 20)	Group without end point (n = 78)	p
Age, years	78.1 ± 7.9	71.4 ± 8.4	0.002
Diabetes mellitus	13 (46%)	26 (38%)	0.42
High blood pressure	23 (82%)	50 (73%)	0.32
Tobacco use	12 (43%)	22 (32%)	0.31
Dyslipidemia	16 (57%)	48 (70%)	0.24
Coronary heart disease	9 (32%)	16 (23%)	0.36
Nonsevere valve disease	6 (21%)	21 (30%)	0.37
Heart failure	4 (14%)	4 (6%)	0.17
P-wave duration ECG, ms	124.7 ± 16	114.8 ± 20	0.05
aIAB	9 (45%)	13 (16.7%)	0.007
Ratio E/e′	12.8 (10.2–15.4)[a]	15.3 (12.5–17.2)[a]	0.03
Tissue Doppler a′, cm/s	7.5 (6.0–9.5)[a]	8.7 (7.7–10.1)[a]	0.03
SRa, s^{-1}	−1.04 ± 0.54	−1.49 ± 0.60	0.003
SRs, s^{-1}	0.68 ± 0.32	0.86 ± 0.30	0.03
Strain in diastasis, s^{-1}	5.80 ± 3.00	7.31 ± 3.77	0.11

Note. Data presented as mean ± *SD* unless otherwise stated.
aIAB: advanced interatrial block; SRa: strain rate at left atrial pump function phase; SRs: strain rate in the left atrium reservoir phase.
[a]Continuous variables that were not normally distributed are presented as median and interquartile interval.

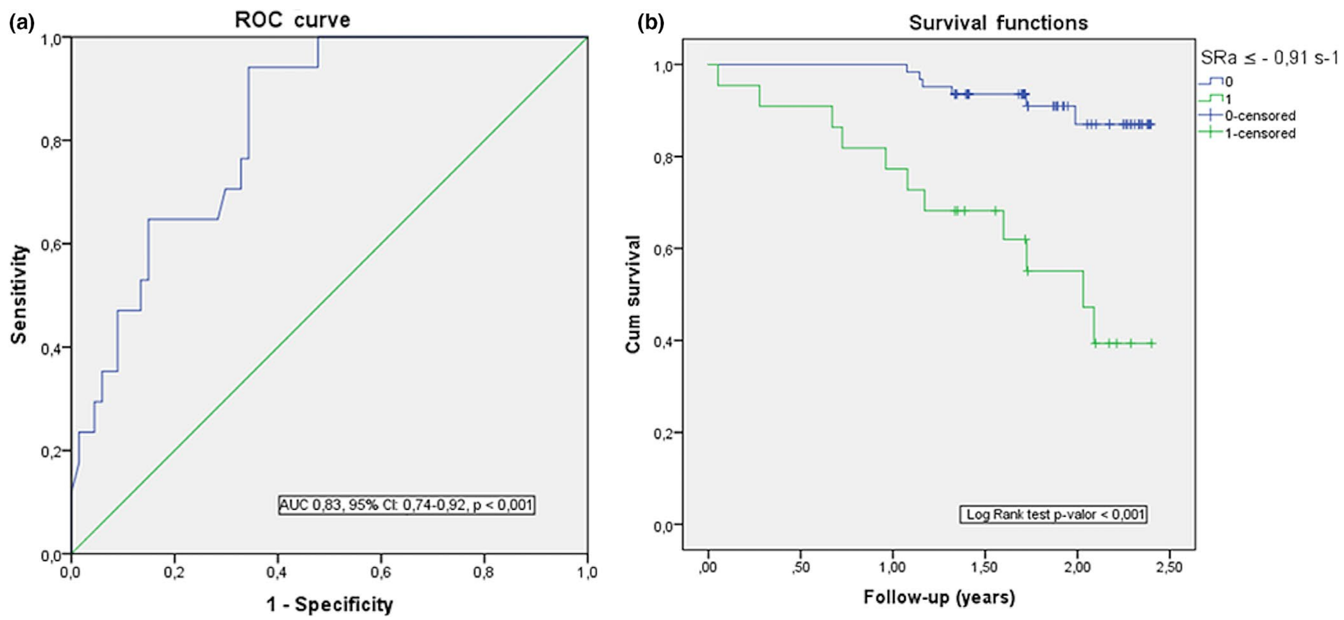

FIGURE 3 ROC curve of SRa showing the power of classification according to the presence or absence of the end point (atrial fibrillation or stroke) (a). Survival curve of Kaplan–Meier according to the presence or absence of an absolute SRa value ≤−0.91 s^{-1} and the appearance in the follow-up of the end point (atrial fibrillation or ictus) (b)

3 | RESULTS

Based on the ECG, three groups were established: 55 control patients (56.2%) with normal ECG without IAB, 21 patients (21.4%) with pIAB and 22 patients (22.4%) with aIAB.

The follow-up period was 1.9 (1.7–2.3) years, with 20 patients presenting the primary end point (18 new AF and two strokes): 8 (14.5%) in the control group, 3 (14.3%) in the pIAB group and 9 (40.9%) in the aIAB group, p = 0.03. Table 1 shows clinical, ECG and STE variables, depending on the presence or absence of the end point. The univariate survival analysis with the Cox proportional risk model for single events showed the following variables associated with the end point: age (hazard ratio [HR] 1.1, confidence interval [95% CI, 1.04–1.17], $p = 0.02$), P-wave duration (ms) (HR 1.03, 95% CI, 1.01–1.05; $p = 0.04$), presence of aIAB (HR 2.97, 95% CI, 1.23–7.17; $p = 0.01$) and SRa, s^{-1} (HR 4.13, 95% CI, 1.43–11.93; $p = 0.009$). With the significant variables of the univariate analysis, we established a multivariate backward stepwise regression analysis. As P-wave duration and the presence of aIAB are correlated, two initial models were defined: (a) age, P-wave duration and SRa and (b) age, presence of aIAB and SRa. In our series, the SRa was the only variable independently related to the appearance in the evolution of the end point. In the first model: HR 19.9 (95% CI, 3.12–127.5), $p = 0.002$, and in the second: HR 24.2 (95% CI, 3.15–185.4), $p = 0.002$. The ROC curve of the SRa adequately classified the patients of our series at the time of presence or absence of the end point, being the discrimination capacity of the SRa high (AUC 0.83, 95% CI 0.74–0.92, $p < 0.001$; Figure 3a). The best cutoff point that identified patients who had or did not have the end point was an absolute SRa $\leq -0.91\ s^{-1}$, with a sensitivity of 65% (95% CI: 41–83) and a specificity of 85% (95% CI: 75–92). This absolute value of SRa $\leq -0.91\ s^{-1}$ determined a higher cumulative incidence of AF or ictus, compared to patients with a higher SRa value (log-rank test, $p < 0.001$; Figure 3b).

4 | DISCUSSION

The main finding of our analysis is that the presence of an absolute value of SRa $\leq -0.91\ s^{-1}$, determined by LA STE of a patient with IAB, determines an increased risk of presenting at follow-up AF and/or stroke, despite the patient having no history of AF. All of this demonstrates in patients with IAB the existence of alterations, not only anatomical, but also functional in the wall of the LA, which favors the risk of AF and stroke, so frequent in this type of patients with aIAB.

The epidemiological study Atherosclerosis Risk in Communities has shown that aIAB is associated with a high risk of AF (HR 3.09, CI 95% 2.51–3.79; O'Neal et al., 2016). Other studies have shown an association between aIAB and increased risk of presenting AF (Escobar-Robledo et al., 2018; Massó-van Roessel et al., 2017). Although aIAB often accompanies LA growth, it is an expression of electromechanical LA dysfunction, inducing abnormal and delayed LA activation, facilitating the formation of microthrombi and thrombus in it, especially in the LA appendage. The importance of atrial fibrosis in this mechanism, as part of fibrotic atrial cardiomyopathy, directly related to endothelial damage and favoring the appearance of AF and the activation of the thrombogenic cascade (Hirsh, Copeland-Halperin, & Halperin, 2015), stands out. Based on this, some researchers have indicated that patients with aIAB presenting: $p \geq 160$ ms, structural heart disease, more than 40 atrial extrasystoles/hr and/or frequent premature atrial complexes in the Holter or CHA2DS2-VASc ≥2, could benefit from the use of early anticoagulation, even without evidence of AF, due to the high risk of AF and stroke (Martínez-Sellés, Fernández Lozano, Baranchuk, Bayes-Genis, & Bayés De Luna, 2016). However, the mere presence of an IAB is not an indication of oral anticoagulation. The emergence of new technologies, as STE, allows a more in-depth study of atrial function in patients with IAB (Lacalzada-Almeida et al., 2018). Our results suggest that the determination in patients with aIAB of a significant decrease in SRa, as an expression of left atrial fibrotic cardiomyopathy (Hirsh et al., 2015), would make it possible to establish a new echocardiographic variable of risk of AF or stroke, complementing the fundamental and determining role of the ECG in the assessment of AF risk in patients with aIAB (Escobar-Robledo et al., 2018; O'Neal et al., 2016; Martínez-Sellés et al., 2016).

4.1 | Limitations

Larger sample size studies would be needed to confirm our results and to evaluate the prognostic usefulness of LA STE in patients with IAB.

5 | CONCLUSION

Our results suggest that the determination in patients with aIAB of a significant decrease in SRa, as an expression of left atrial fibrotic cardiomyopathy (Hirsh et al., 2015), would make it possible to establish a new echocardiographic variable of risk of AF or stroke, complementing the fundamental and determining role of the ECG in the assessment of AF risk in patients with aIAB (Escobar-Robledo et al., 2018; O'Neal et al., 2016; Martínez-Sellés et al., 2016).

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHORS' CONTRIBUTION

ABL, AB and JLA involved in conception and design of the work. JGN, MMIG and JLA wrote the case description and involved in critical revision of the work. RE, AJS and JLA involved in the methodological and statistical design of the study. All authors were involved at each stage of the revision process and contributed substantially to the project's intellectual content.

ORCID

Juan Lacalzada-Almeida https://orcid.org/0000-0002-9863-3222

María Manuela Izquierdo-Gómez https://orcid.org/0000-0002-6379-9820

Javier García-Niebla https://orcid.org/0000-0003-2851-5885

Roberto Elosua https://orcid.org/0000-0001-8235-0095

Alejandro Jiménez-Sosa https://orcid.org/0000-0001-8732-2616

Adrian Baranchuk https://orcid.org/0000-0002-3042-6569
Antonio Bayes de Luna https://orcid.org/0000-0003-1676-207X

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